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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,168	09/24/2003	Krista Evans	0942.402003	5379

26111 7590 10/30/2006

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EXAMINER	
SLOBODYANSKY, ELIZABETH	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/668,168	EVANS, KRISTA	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 4, 2006 has been entered.

The amendment filed October 4, 2006 canceling claims 1-22 and adding claims 23-42 has been entered.

Claims 23-42 are pending.

Claim Objections

Claim 41 is objected to because of the following informalities: it depends from claim 32 where it appears claim 33 is intended. In the interests of the compact prosecution claim 41 was construed as if it were properly written, i.e. dependent from claim 33.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 26-33 and 36-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 23, with dependent claims 26-32, and claim 33, with dependent claims 36-42, are drawn a nucleic acid encoding a mutant *Aequorea victoria* GFP that is mutated at a single position 64 where cysteine substituted for phenylalanine at position 64 (F64C). Applicants indicates support for claims 23 and 33 "at least at paragraph [0024] of the specification as filed" (Remarks of 10/4/06, page 5). Applicant further cites the specification "The invention is particularly directed to such nucleic acid molecules encoding mutant GFPs, wherein the amino acid residue at position 64 is alanine, valine, leucine, isoleucine, proline, methionine, glycine, serine, threonine, cysteine, alanine, asparagine, glutamine, aspartic acid, or glutamic acid, most preferably cysteine or methionine. Further support is provided in the mutants of Table 3, for example, pGreenLantern-2/A2 and pGreenLantern-2/A3" (Remarks of 10/4/06, page 6). The Examiner does not agree. It is apparent that the quoted text describes a specific position in the double mutants discussed on the preceding lines of the same paragraph. Furthermore, the entire content of the application is not related to a single F64 mutant.

For example, pGreenLantern-2/A2 and pGreenLantern-2/A3 (Table 3, page 31) contain double mutants F64C/S65T and F64L/S65T, respectively. In view of the fact that the current claims recite F64C mutation, Applicant probably meant to recite pGreenLantern-2/A1 that has double mutation F64C/S65A (Table 3). In any event, nowhere in the specification, including in Table 3, a singe F64C mutant is described. There is no indication that the GFP mutant with a single F64C mutation was within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24, 25, 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 and claim 34 are dependent on claims 23 and 33, respectively. Claims 23 and 33 recites a GFP mutant having a single substitution F64C. Claim 24 is drawn to the nucleic acid molecule of claim 23, which said mutant Green Fluorescent Protein is mutated at amino acid position 65 of SEQ ID NO:4. Claim 24 is confusing as drawn to the nuclei9c acid of claim 23because claim 23 recites only one mutation in SEQ ID NO:4, wherein claim 24 recites the second mutation at position 65. Similarly, claim 34.

Claims 25 and 35 are rejected as dependent from the rejected base claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23 and 26-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michaels.

Michaels (US Patent 6,096,865) teaches F64L mutant of *Aequorea victoria* GFP, a vector and a host comprising thereof. The inventor teaches that said mutant has improved fluorescent properties under standard physiological conditions for human cells at 37^{O} C (abstract; column 5, lines 28-67; column 8, lines 56-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce single F64 GFP mutants wherein phenylalanine is replaced by any of the remaining 18 amino acids, including cysteine. One of ordinary skill in the art would have been motivated to do so in order to find single F64 GFP mutants that have similar or different fluorescent properties because such mutants can be used for protein localization and trafficking. One of ordinary skill in the art would have a reasonable expectation that other single F64 GFP mutants, including F64C would have useful fluorescent properties. Furthermore, testing of all 18 possible F64 GFP mutants does not require undue experimentation in view of the limited number of the GFP mutants that can be made.

Claims 33 and 36-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michaels. in view of Zolotukhin et al.

The teachings of Michaels are outlined above.

Zolotukhin et al. (form PTO-1449 filed July 9, 2004, reference AS8) teach humanized cDNA encoding wild type GFP and S65T mutant thereof (page 4649, 1st column, last full paragraph). The humanized DNA enhances the efficiency of translation and hence expression up to 22-fold in mailman cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce any GFP mutant, including a single F64 GFP mutant, using humanized cDNA taught by Zolotukhin et al. One of ordinary skill in the art would have been motivated to do so in order to achieve high-level expression in mailman, including human, cells.

Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cormack et al.

Cormack et al. (US Patent 5,804,387, form PTO-1449 filed July 9, 2004, reference AD1) teach that "Mutants with Ala, Gly, Ile, Cys or Thr substituted for Ser65 had large shifts in excitation maxima, and fluoresced more intensely than wild-type protein when excited at 488 nm" (column 2, lines 22-25). They further teach that "The mutation of Ser65 to Thr or Cys was observed to increase by a factor of 6 the fluorescence of GFP following 488 nm excitation" (column 2, lines 44-46, and Table 1).

Cormack et al. teach a set of mutations at positions comprising S65 and F64 (column 3, lines 1-3). They teach that "the set of positions consists of all amino acid positions in the mutant GFP in which an amino acid differs from the corresponding amino acid of wild-type GFP" (column 3,lines 3-6). They explicitly teach GFP mutant F64L/S65T (GFP mut1) and DNA encoding thereof that has enhanced fluorescence compared with the wild type GFP and a single mutant (abstract; Figures 4-5; column 9, Table 4). They teach vectors, host cells comprising DNA encoding such GFP mutants and methods for producing said mutants.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce double GFP mutants comprising S65A, S65T or S65C coupled with any amino acid substituted for F64, including F64C/S65T. One of ordinary skill in the art would have been motivated to do so in order to find double 64/65 GFP mutants that have similar or different fluorescent properties because such mutants can be used for protein localization and trafficking. One of ordinary skill in the art would have a reasonable expectation that other double 64/65 GFP mutants with possible slight variations would have useful fluorescent properties. Furthermore, testing of even all possible 64/65 GFP mutants does not require undue experimentation in view of the limited number of the double 64/65 GFP mutants that can be made.

Claims 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cormack et al. in view of Zolotukhin et al.

The teachings of Cormack et al are outlined above.

Zolotukhin et al. (form PTO-1449 filed July 9, 2004, reference AS8) teach humanized cDNA encoding wild type GFP and S65T mutant thereof (page 4649, 1st column, last full paragraph). The humanized DNA enhances the efficiency of translation and hence expression up to 22-fold in mailman cells. In addition, a S65T mutation in humanized GFP DNA results in 5 to 10 fold increase over humanized wild-type (page 4649, Figure 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce double F64/S65 GFP mutants, including F64C/S65T, using humanized cDNA taught by Zolotukhin et al. One of ordinary skill in the art would have been motivated to do so in order to achieve high-level expression in mailman, including human, cells.

Response to Arguments

Applicant's arguments filed October 4, 2006 have been fully considered but they are not persuasive.

The outstanding objection and 112, 1st paragraph, rejection are withdrawn in view of the amendment.

With regard to the 103(a) rejection, Applicants argues that "New independent claim 23 (from which new claims 24-33 depend) recites a mutant GFP in which the amino acid residue at position 64 is cysteine. Applicant contends that cysteine, an amino acid that is not a conservative substitution of the amino acid {phenylalanine) that is present at position 64 of the wild-type protein, is a nonobvious alteration of the GFP

protein which results in GFP mutants having unexpected properties of fluorescence more intense than the wild-type GFP (as provided in Table 3 of the application) (Remarks of 10/4/06, page 7). These arguments are not persuasive. The importance of F64 is known in the art. The improved properties of GFP mutant F64L/S65T is known in the art. It is obvious to make substitutions at position 64 either in a single or in a double mutant with all remaining 18 amino acids. Furthermore, F64C/S65T mutant does not display any unexpected properties because while its fluorescence is more intense than the wild-type GFP (Table 3 of the application), it is due to S65T mutation as can be construed by comparison of pGreenLantern-1 (F64/S65T) with pGreenLantern-2/A2 (F64C/S65T), which both display 22 fold increase in intensity over wild type (Table 3, page 31).

With regard to the 103(a) rejection over Cormack et al. in view of Zolotukhin et al., Applicant argues "New independent claim 34 (from which new claims 35-44 depend) recites a humanized nucleic acid molecule encoding a mutant GFP in which the amino acid residue at position 64 is cysteine. To establish a prima facie case of obviousness there must be some suggestion or motivation in the prior art to make the claimed invention, there must be a reasonable expectation of success, and the prior art reference must teach or suggest all of the claim limitations. MPEP 2142; In re Vaeck, 947 F.2d 488, 20 USPQ2d, 1438 (Fed. Cir. 1991). Cormack ('387) and Zolotukhin et al. do not, alone or in combination, teach or suggest cysteine at amino acid position 64 of a Green Fluorescent Protein mutant, or a nucleic acid encoding a F64C mutant of GFP. Thus, each element of the claim is not present in the cited art, and the claims are

patentable under 35 U.S~C. §103(a)" (page 8). It is not agreed that F64C is non-obvious. F64L has greatly improved properties. It would have been obvious to replace F64 with only 18 amino acids in order to find mutants with useful properties. Furthermore, Applicant does not teach any unexpected properties of F64C absent of which said mutant is obvious. In addition, while mutant F64C/S65T is not disclosed in Cormack et al., the rejection is 103(a) not 102. As a reference in the 103(a) rejection, that reference does not have to disclose the same invention but only to make it obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

October 25, 2006